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Great Lakes Water Quality Seventh Annual Report 1978: Appendix G Annual Report of the Committee on the Assessment of Human Health Effects of Great Lakes Water Quality

Great Lakes Water Quality Board. Committee on the Assessment of Human Health Effects of Great Lakes Water Quality

Great Lakes Science Advisory Board

GREAT LAKES
WATER QUALITY BOARD
SCIENCE ADVISORY BOARD

INTERNATIONAL JOINT COMMISSION

GREAT LAKES WATER QUALITY 1978
APPENDIX G
ASSESSMENT OF HUMAN HEALTH EFFECTS

GREAT LAKES WATER QUALITY

SEVENTH ANNUAL REPORT

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PREFACE

The 1978 Annual Report of the International Joint Commission's Committee on the Assessment of Human Health Effects of Great Lakes Water Quality was prepared both for the Water Quality Board and for the Science Advisory Board.

Highlights from the activities of the Committee, from its inaugural meeting, early in 1978 to the present, are reported here.

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INTRODUCTION

One of the most important recommendations contained in the Sixth Annual Great Lakes Water Quality Report of the International Joint Commission (1978) has urged that the Governments of the United States and Canada "collaborate and develop a program which establishes a running inventory of toxic chemicals used, manufactured or imported into the Great Lakes Basin" and "evaluate their risk to human health and the environment." As a result of its continuing and growing concern over the potential human health hazards of contaminants which bioaccumulate in fish, a special committee on the Assessment of Human Health Effects of Great Lakes Water Quality was formed in early 1978.

TERMS OF REFERENCE

In considering its mandate, the committee proposed and agreed to take the following under its purview:

1. Assess the risk to health posed by contaminants in the Great Lakes ecosystem.

2. Review action levels and guidelines for selected substances.

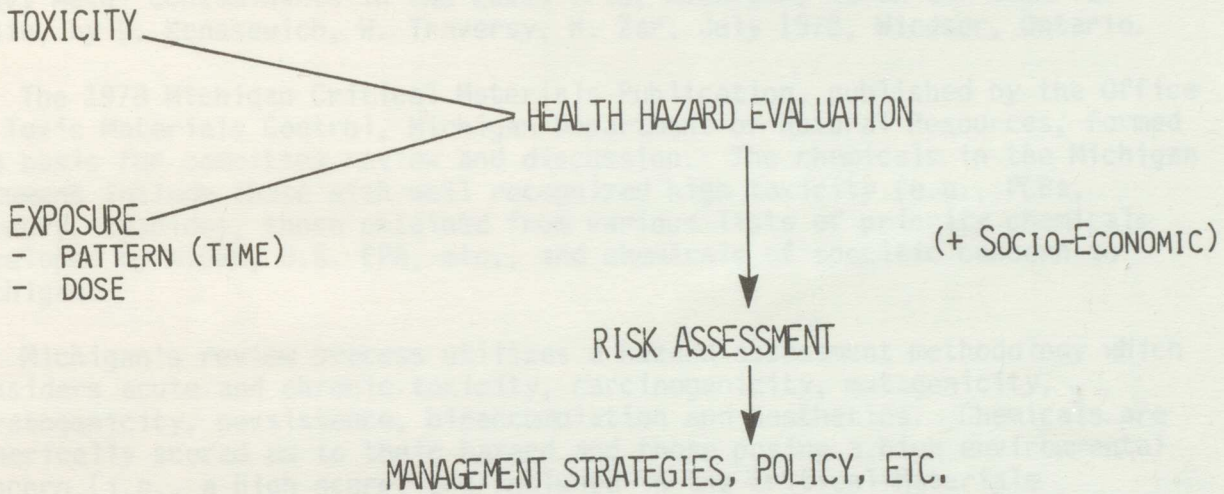
3. Provide to the International Joint Commission through its Boards, interpretation and consultation on health matters.

4. Maintain awareness of current advances and knowledge as they relate to human health aspects of the ecosystem.

The result of the inaugural meeting of this committee was a decision to review the 1975 Water Quality Board's Appendix E, "Status Report on the Persistent Toxic Substances in the Lake Ontario Basin." The compounds selected for study initially were lead and mirex.

1 HEALTH HAZARD EVALUATION

This process is viewed by the committee as depicted in the schematic diagram below:



Chapter 2 on Toxicity Evaluation in this report identifies the categories used to select chemicals posing human health hazards and provides an appropriate "scoring" system. Also, Chapter 3 on Human Exposure explores the routes for environmental contamination by these chemicals.

2 TOXICITY EVALUATION

The committee, at its October 1978 meeting, discussed the problem of establishing criteria for rating the hazards presented by the 400 chemicals recently identified in the Great Lakes by the Great Lakes Water Quality Board; see Great Lakes Water Quality Board - Appendix E, Status Report on Organic and Heavy Metal Contaminants in the Lakes Erie, Michigan, Huron and Superior Basin, by D. Konasewich, W. Traversy, H. Zar, July 1978, Windsor, Ontario.

The 1978 Michigan Critical Materials Publication, published by the Office of Toxic Materials Control, Michigan Department of Natural Resources, formed the basis for committee review and discussion. The chemicals in the Michigan document include those with well recognized high toxicity (e.g., PCBs, mercury, cyanide), those obtained from various lists of priority chemicals developed by NIOSH, U.S. EPA, etc., and chemicals of specific concern to Michigan.

Michigan's review process utilizes a hazard assessment methodology which considers acute and chronic toxicity, carcinogenicity, mutagenicity, teratogenicity, persistence, bioaccumulation and aesthetics. Chemicals are numerically scored as to their hazard and those posing a high environmental concern (i.e., a high score) are included in the Critical Materials Publication. Table 9 - "Critical Materials Register Hazard Assessment Sheet," is reproduced below from the Michigan publication.

The Human Health Effects Committee selected the following categories:

- acute toxicity;
- carcinogenicity;
- reproductive;
- heritable mutagenicity;
- neurobehavioural toxicity; and
- chronic adverse effects.

I. ACUTE TOXICITY

Criterion:

Score	Oral LD_{50}	Dermal LD_{50}
4 Extremely Toxic	<5 mg/kg	<5 mg/kg
3 Highly Toxic	5-50 mg/kg	5-200 mg/kg
2 Moderately Toxic	<50-500 mg/kg	<200-500 mg/kg
1 Slightly Toxic	<0.5-5 g/kg	<0.5-5 g/kg
0 Relatively Non-Toxic	<5 g/kg	<5 g/kg
* Insufficient information		

Table 9.

Michigan
Critical Materials Register Hazard Assessment Sheet

Common Chemical Name _____
Chemical Abstract Name _____

Chemical Abstract No. _____

I. Acute Toxicity — Score _____

Score	ORAL LD50 mg/kg	DERMAL LD50 mg/kg	AQUATIC 96 HOUR LD50 mg/l
7	<5	<5	<1
3	5-50	5-200	1-10
2	>50-500	>200-500	>10-100
1	>500-5000	>500-5000	>100-1000
0	>5000	>5000	>1000
*	Insufficient Information		

II. Carcinogenicity _____

Score	Category
7	Human positive human suspect Animal positive
3	Animal suspect
2	Carcinogenic by a route other than oral or dermal Strongly potential carcinogenic by accepted mutagenicity screening tests or accepted cell transformation studies
1	Potential carcinogen by accepted mutagencity screening tests or accepted cell transformation studies
0	Not carcinogenic
*	Insufficient Information

III. Hereditary Mutagenicity _____

Score	Category
7	Confirmed
4	Suspect - multicellular organisms
2	Suspect - micro-organisms
0	Not a hereditary mutagen
*	Insufficient Information

IV. Teratogenicity _____

Score	Category
7	Confirmed
3	Suspect
0	Not teratogenic
*	Insufficient Information

V. Persistence _____

Score	Category
4	Very persistent
3	Persistent
2	Slowly degradable
1	Moderately degradable
0	Readily degradable
*	Insufficient Information

VI. Bioaccumulation _____

Score	Bioaccumulation	Log P
7	>4000	>6.00
3	1000-3999	5.00-5.99
2	700-999	4.50-4.99
1	300-699	4.00-4.49
0	<300	<4.00
*	Insufficient Information	

VII. Aesthetics _____

Score	Category: Fish Tainting/Tase and Odor (Threshold level in water - mg/l)	Category: Foaming, floating film, and/or major colour change
3	0.0001-0.001	
2	>0.001-0.01	
1	>0.01-0.1	Yes
0	>0.1	No

VIII. Chronic Adverse Effects _____

Score	Category
4	Irreversible effects
2	Reversible effects
1	Adverse effects by route other than oral, dermal, or aquatic
0	No detectable adverse effects
*	Insufficient Information

Rationale:

Classification is based upon generally accepted terminology found in the available literature on acute toxicity.

In review of the literature referenced below, dealing with the classification of toxicants, never was less than 50 mg/kg considered moderately toxic. In EPA's TSCA criteria for acute toxicity, 50 to 500 mg/kg is classified as "very toxic" as is one of the systems described by Hodge and Sterner (1949) and Gleason (1969).

The critical levels describing "highly toxic" for oral, dermal, and aquatic LC_{50}s are adapted from Battelle Memorial Institute, National Academy of Sciences, State of California List of Toxic Substances, Federal Water Pollution Control Agency, Pesticides-Title 40, Department of Transportation Title 49, Consumer Product Safety Commission, and the Federal Hazardous Substances Labeling Act Title 15 classifications, as well as systems presented by Hodge and Sterner (1949). Levels of "moderate," "slightly" and "relatively nontoxic" are adapted from the National Academy of Sciences, and Hodge and Sterner (1949).

Data available for each category for each type of exposure (i.e., oral, dermal, aquatic) is scored independently. The score assigned to the acute toxicity factor is the highest score given to any individual category. For example, a chemical substance which has an oral LD_{50} of 5-50 mg/kg, a dermal LD_{50} of 200-500 mg/kg, and an aquatic 96 hour LC_{50} of less than 1 mg/kg is assigned a score of seven, based on the extreme aquatic toxicity.

References

Cassarett, L. J.; Doull, Jr., Toxicology, The Basic Science of Poisons; Macmillan Publishing Co., Inc., New York, 1975.

Gleason, M. N.; Gosselin, R.E.; Hodge, H.C.; and Smith, P.R.; Clinical Toxicology of Commercial Products, 4th Ed., Williams & Wilkins Co., Baltimore, 1977.

Hodge, H.C. and Sterner, S.H., Tabulation of Toxicity Classes, AIHA Quarterly 10:93-96, 1949.

Kohen, A.M., A Summary of Hazardous Substance Classification Systems (SW-171). U.S. EPA, 1975.

U.S. EPA, Initial Report of the TSCA Interagency Testing Committee to the Administrator, Environmental Protection Agency, Jan. 1978.

I(A) Potency:

Criterion:

	Weighting Factor
Strong	X2
Weak	X1

This factor is applied in all categories other than acute toxicity.

Rationale:

Except in the acute toxicity category, the concept of dose to produce a stated effect is absent in the foregoing scoring system. However, it is recognized that materials do vary in their potency and that very potent substances create greater concern and demand priority consideration over less potent materials that may evoke the development of similar qualitative effects but only after much higher does have reached the target cells, organs or organisms, and often only after longer periods of time.

To account for differences in potency, the rating accorded a substance under any toxicity category is doubled if the material is judged to possess strong potency.

The distinction between "strong" and "weak" potency with respect to carcinogens has been maintained for many years. Weak carcinogens are those which manifest their effects only after repeated dosage over a long period of time, often at doses which produce other tissue damage or which induce other effects such as altered metabolic processes. Strong carcinogens, on the other hand, induce neoplasia with much lower doses, sometimes even with a single exposure; latent periods may be shorter and the carcinogenic response is frequently evoked without other concomitant pathological change.

II. CARCINOGENICITY

Criterion:

Score	Category
4	The chemical has been demonstrated to be a human positive carcinogen (defined in (a) below) by the oral, dermal or inhalation route of exposure.
2	The chemical has been demonstrated to be a suspected carcinogen (defined in (c) below) by the oral, dermal, or inhalation route of exposure.
1	The chemical has been demonstrated by accepted mutagenicity screening tests or accepted cell transformation studies to be a potential carcinogen (defined in (d)).
0	The chemical has been tested by the above systems and has not been demonstrated to cause cancer or to be a potential

carcinogen.

* Insufficient information available.

Rationale:

Most cancers are believed to be caused by exposure to extrinsic factors, among which chemical agents are thought to be a major contributor. These agents must be identified, evaluated, and controlled if the incidence of cancer is to be reduced. The committee recognizes the need to protect the public and the environment from chemical carcinogenic hazards and their effects. In an effort to meet this need, the above carcinogenicity criterion was developed.

It is essential that the procedures used to determine a chemical's carcinogenicity potential be established on the best scientific basis as is practically possible. For the purpose of classification, chemicals will be placed in categories relating to carcinogenic effects. If insufficient information is available to classify a chemical, it will be so noted. The chemical can be reclassified in an appropriate category when additional data become available.

The catagories of carcinogenic effects are defined as follows:

(a) Human Carcinogen

- Chemical which has been demonstrated by epidemiological and/or clinical studies to cause cancer in man.

(b) Positive Animal Carcinogen

- Chemical which has been found and confirmed to be carcinogenic in animals. (If observation has been made only in mice, see (c) below.)

(c) Suspected Animal Carcinogen

- Chemical which has been found to be carcinogenic in one series of well designed experiments and found to be non-carcinogenic in repeated experiments, but no explanation is apparent to account for the discrepancies between positive and negative results.

- Chemical which has been found to be carcinogenic in mouse only but not confirmed in another species.

(d) Positive <u>In Vitro</u> Test Carcinogen

- Chemical which has been found by mutagenicity tests (with or without enzyme activation) to demonstrate carcinogenic potential.

- Chemical which has been shown to transform normal human or normal mammalian cells into tumour cells in replicated tests designed to demonstrate carcinogenic potential.

III. REPRODUCTIVE,
IV. HERITABLE MUTAGENICITY

(i.e., teratogenicity and foetal toxicology)

1. teratogenic effects.
2. foetal toxicity.
3. embryotoxicity.

pathology, behaviour

Criterion:

Score	Category
4	Confirmed teratogen
2	Suspect teratogen in multicellular organisms
1	Suspect mutagen in microorganisms
0	Not demonstrated to be a mutagen
*	Insufficient information

V. NEUROBEHAVIORAL TOXICOLOGY

Criterion:

Neurotoxicity and the potential of a chemical to cause behavioral changes in mammals or other animals will be assessed according to the following scores:

Score	Category
4	Confirmed human neurotoxic chemical
3	Confirmed animal neurotoxic agent, therefore suspect in humans
1	Suspect animal neurotoxic chemical
0	No neurotoxic activity
*	No information

Rationale:

Score	Category
4	Chemicals known to cause nervous system malfunctions and/or pathology, behavioral disorders including learning disabilities in humans, will be considered as confirmed neurotoxic agents for humans.
3	Chemicals causing neuropathies in experimental animals will be considered suspect neurotoxic agents for humans.
1	Chemicals shown to cause only behavioral changes in animals will be considered potentially suspect neurotoxic agents for animals.

0 A chemical, adequately tested for neurobehavioral toxicity with negative findings will be considered inactive as a neurotoxic agent.

* Where insufficient information is available testing should be considered.

Score	Category
4	Confirmed human neurotoxic chemical
3	Confirmed animal neurotoxic agent, therefore suspect in humans
1	Suspect animal neurotoxic chemical
0	No neurotoxic activity
*	No information

VI. CHRONIC ADVERSE EFFECTS

Introduction and Rationale:

The category "Chronic Adverse Effects" contains a large variety of toxic effects on a variety of target organs and tissue. Some have been left out because they were considered unlikely to be affected by chemicals in the water of the Great Lakes. Wherever possible however the systems are included and scores proposed with occasional examples, which may be deleted.

The wording is usually too short and thus unclear. When effects are observed they are adverse irreversible effects unless otherwise stated. When effects are not observed in humans, but only in animals, it does not mean that the effects were lacking in humans exposed to the chemicals, but rather that humans were not exposed to the chemicals. Human data are obtained from epidemiological studies and not from clinical reports only, which may be erroneous in the association proposed.

When no adverse effects are observed it means that no serious adverse effects are found. Weight loss can always be produced with a high enough dose with any choice of chemical, but that is not meant here.

No attention was paid to genetic weakness of human populations, although the means to do so exist. However, in experiments on animals it has frequently been the custom to choose a strain that would display genetic susceptibilities in order to exaggerate the effect. Although this is permissible it should be recognized as such and given a particular recognition, since extrapolation to the normal human population would be impossible or difficult.

Criterion:

(a) Sense Organs

Score	Category
	N.B. Unless specified the effects are irreversible and/or progressive
3	Effects observed in humans (e.g., cataracts)
2	Effects not observed in humans, but on experiments in animals

1 Reversible effects observed in humans or animals
0 No adverse effects observed
* No information

Some effects of chemicals may be caused by interference with nerve function or toxicity to the nerve itself and will be classified under category V.

(b) Hepatobiliary System

Score	Category
3	Effects observed in humans (e.g, cirrhosis, bileduct hyperplasia)
2	Effects not observed in humans, but in animal experiments
1	Reversible effects observed in humans or animals (e.g., bilirubinemia)
0	No adverse effects observed
*	No information

Reversible effects should be distinguished from effects which may also be reversible because, after the necrotic episode is over, regeneration can replace the lost tissue.

(c) Urinary System

Score	Category
3	Effects in humans
2	Effects not observed in humans, but in animal experiments
1	Reversible effects in humans or animals
0	No effects observed
*	No information

It is suggested including in these categories adverse effects observed, as for instance, with NTA which produced tubular damage to the kidney at relatively low levels and which produced renal cancers at very high dose levels which would also be reported of course under category II.

(d) Cardio-vascular system

Score	Category
3	Effects observed in humans
2	Effects not observed in humans, but in animal experiments
1	Reversible effects observed in humans or animals
0	No effects observed
*	No information

A weighting factor of 2x is proposed for the adverse effects of this chemical if the impaired health (due to other causes) will considerably aggravate the toxicity of the chemical. The same consideration applies to the respiratory system and the lymphatic system.

(e) Respiratory System

Score	Category
3	Effects observed in humans
2	Effects not observed in humans, but in animals in experiments
1	Reversible effects observed in humans or animals
0	No effects observed
*	No information

A weighting factor of 2x is proposed here also even though the contribution of chemicals via the Great Lakes to the respiratory system may be rare or unlikely. The conditions of impaired health may include emphysema, edema, fibrosis, etc.

(f) Blood Forming System

Score	Category
3	Effects in humans, e.g., porphyrias
2	Effects not observed in humans, but in animal experiments
1	Reversible effects in humans or animals
0	No effects observed
*	No information

(g) Lymphatic System

Score	Category
3	Effects in humans, e.g., immunopathology
2	Effects not observed in humans, but in animal experiments
1	Reversible effects in humans or animals including chromosomal abnormalities
0	No effects observed
*	No information

(h) Endocrine System

Score	Category
3	Effects in humans
2	Effects not observed in humans but in experimental animals
1	Reversible effects in humans or animals
0	No effects observed
*	No information

This subcategory should include adverse effects on the hypothalamus and the pituitary gland as well as the endocrine organs under pituitary control and target organs under the influence of specific hormones. The subcategory may also have to contain the effects of chemicals secreted by the mammary gland and affecting the young offspring.

(i) Reproductive System

Score	Category
3	Effects in humans, e.g., sterility
2	Effects not observed in humans but in experimental animals
1	Reversible effects observed in humans or animals

0	No effect observed
*	No information

This category may also contain the effects of chemicals binding to encephalin-receptors, e.g., potential loss of libido

(j) Gastro-Intestional System

Score	Category
3	Effects observed in humans
2	Effects not observed in humans, but experimental animals
1	Reversible effects in humans or animals
0	No effects observed
*	No information

A weighting factor of 2x may have to be applied in this subcategory because impairment of normal function may lead to aggravated responses to chemicals entering the G.I. tract.

(k) Skin

Score	Category
2	Effects observed in humans
1	Effects observed in animals which may be reversible or irreversible
0	No effects observed
*	No information

A weighting factor of 2x may be applicable under conditions of impairment producing abnormal absorption of chemicals or aggravation of effect.

The committee is currently evaluating the 400 compounds identified in the Water Quality Board's report (loc. cit) utilizing the above categories of criteria and scoring systems.

3 ESTIMATES OF HUMAN EXPOSURE FROM ENVIRONMENTAL DATA

Possible health effects of Great Lakes water quality from any chemical compound or agent are a function of both the toxic (carcinogenic) properties of the compound and the possible exposure of man to it.

In order to be concerned about a compound, we consider exposure of any identifiable group of people, however small, and in any area in the Great Lakes Basin, however limited in size.

Exposure is determined by:

1. Inputs into the Great Lakes and the resulting concentrations in the several compartments of the Great Lakes ecosystem.

2. Rates of transformation and translocation within and between compartments.

3. Intake by man of water or food from these compartments.

Beginning with point (3) we identify the following target populations:

(a) Any local population deriving their drinking water from the Great Lakes.

(b) Any local population deriving a substantial portion of their total food intake from Great Lakes fish.

(c) Any local population consuming waterfowl (hunters and their families).

(d) Any local population deriving a significant portion of their food from land irrigated with Great Lakes water or from livestock drinking Great Lakes water.

The following additional target populations are recognized as part of the greater ecosystem of the Great Lakes but are excluded from considerations of Great Lakes water quality.

(e) Local populations deriving food from land receiving wastewater sludges.

(f) Populations exposed in the occupational, domestic, and urban environment to contaminants identified in Great Lakes water and traceable to land sources.

Exposures from (e) to (f) must be taken into account also in determining total exposure of a local population to the contaminant.

Input and concentration data are the points of departure for estimates of exposure. They are shown in boxes in Figure 1, below. Input data are

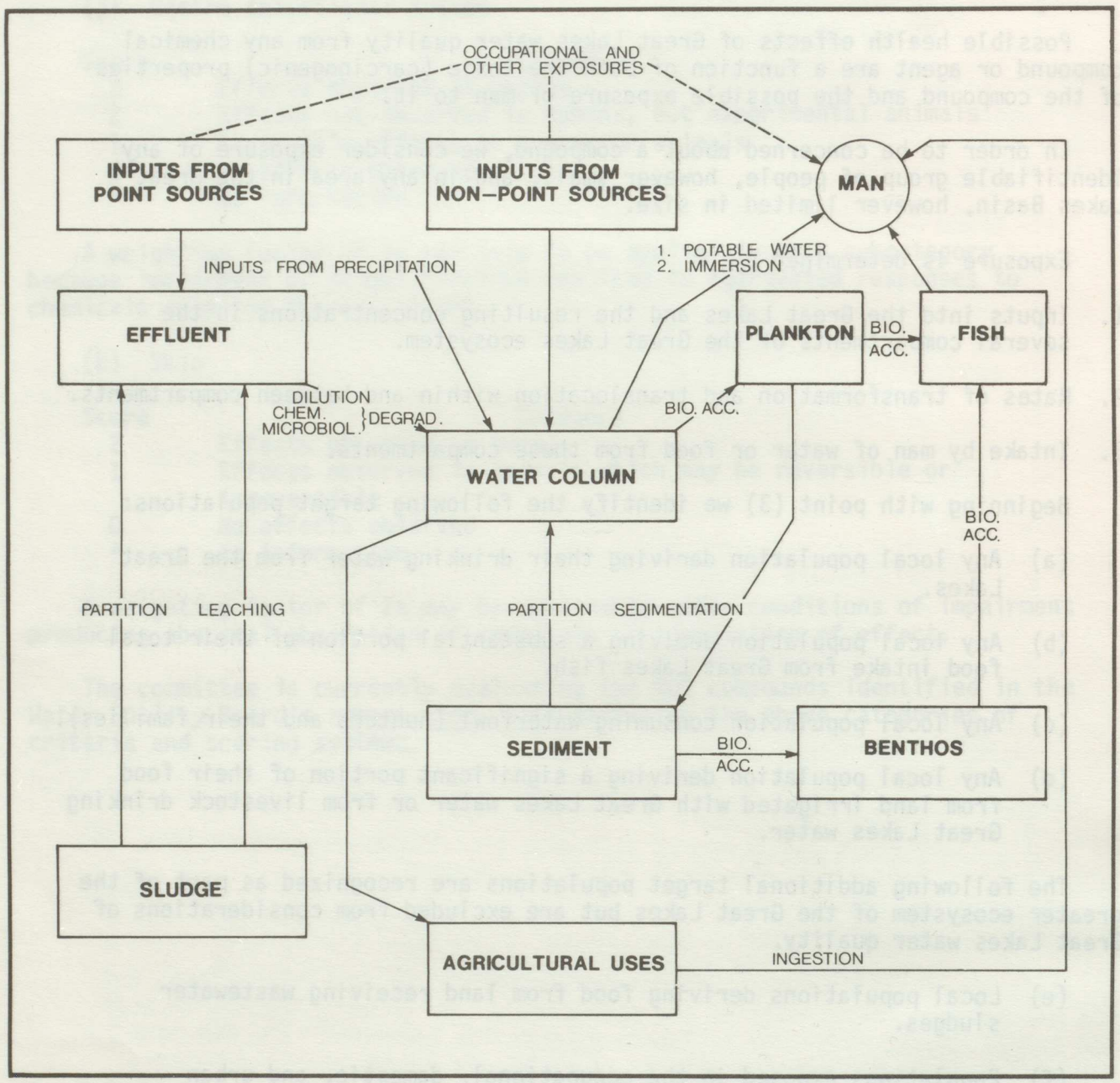

OCCUPATIONAL AND
OTHER EXPOSURES
INPUTS FROM
POINT SOURCES
INPUTS FROM
NON–POINT SOURCES
MAN
INPUTS FROM PRECIPITATION
1. POTABLE WATER
2. IMMERSION
EFFLUENT
PLANKTON
BIO.
ACC.
FISH
DILUTION
CHEM.
MICROBIOL.
DEGRAD.
BIO. ACC.
WATER COLUMN
BIO.
ACC.
PARTITION
LEACHING
PARTITION
SEDIMENTATION
SEDIMENT
BIO.
ACC.
BENTHOS
SLUDGE
AGRICULTURAL USES
INGESTION

Fig. 1

available from measurements of concentrations and flows, or from estimates of production, use, and loss of chemicals. Input data are related to concentration data by factors such as dilution, partition, chemical or microbial degradation, bioaccumulation, etc., (marked by arrows in Figure 1).

For some compounds, the data base available involves numerous measurements of the compounds in several compartments over a large part of the Great Lakes Basin. For other compounds, data are sparse and are available only for limited areas and few, or one compartment of the ecosystem. For the areas known to show measurable concentrations of the compounds, order-of-magnitude estimates of concentrations in other compartments in the same area can be made by applying conversion factors on dilution, partition, degradation, and bioaccumulation. Extrapolation to other areas in the basin is difficult and would be based on known patterns of production and use of chemicals, generalizations on likely sources, etc. In order to undertake this effort, the group recommends the reworking of the available data base (Great Lakes Water Quality Board - Appendix E, Status Report on Organic and Heavy Metal Contaminants in the Lakes Erie, Michigan, Huron and Superior Basins, IJC, Windsor, Ontario, July 1978) into a more useful format giving for each compound, the available data by geographic location and by compartment (amount discharged or effluent concentration measured, concentration in sludge, concentration in water, concentration in sediment, concentration in fish, concentration in other biota). This information will then be analyzed by the above procedures to derive estimates of exposure for any of the possible target populations.

This estimate of the exposure together with data on toxicity, including factors such as carcinogenicity, persistence in man, etc., for each compound will produce a measure of concern by the committee for public health effects from any given compound, refined as is possible by estimates of synergistic and other interactions among compounds. If effect levels are known for a compound, the ratio of exposure level to effect level is a measurement of the public health concern.

The logical sequence of this procedure is summarized in Figure 2, below.

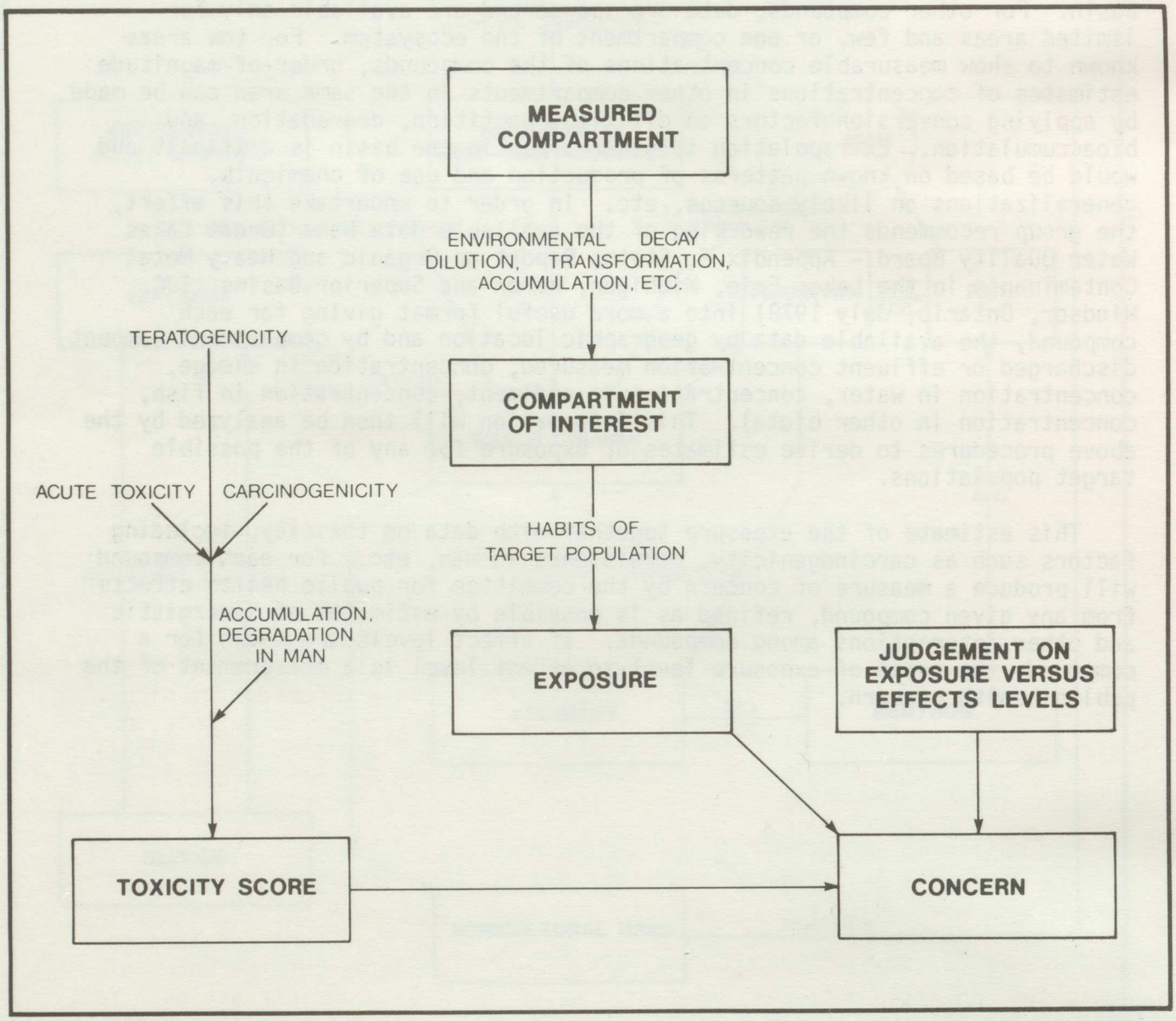


Fig. 2

In many cases the available data will not permit a decision on possible health concern with sufficient certainty, and a call for additional data may result.

4 INTERACTIONS IN TOXICOLOGY: AN OVERVIEW

Interactions in drugs as suggested in the translation of the Papyrus Ebers is an ancient interest (Rossi, '63). The course of history of interactions in toxicology would run parallel to that for drugs since no drug is free of toxic effects (Fingl and Woodbury, '70). Accumulated knowledge of drug interactions, however, is much greater than interactions in toxicology (James, et al., '78). This latter statement would be expected when one considers the age difference between these two sciences. Man, not necessarily man the scientist, has been interested for centuries in the basic effect of a poison. How it worked, or interacted, was not his concern as long as the measured effect, death, was achieved. From that simple observation of yesterday, scientists today are turning more earnestly to the "question of interaction of the causes" (Rothman, '76).

Interactions in toxicology are no longer viewed as a basic biochemical event but they are recognized as complex, complicated and controversial. Assessment of a toxicant is interrelated to nutrition, stress, age, sex, genetics, prior or concurrent diseases, body weight, route of administration, its pharmacokinetics and the environment. With so many diverse factors affecting the observed effect the underlying mechanism becomes very difficult to solve or understand (i.e., complicated). Controversies will undoubtedly arise because most interactions in toxicology have not been resolved. Foremost among these controversies are the problems of interactions with minute or large dosages of a chemical carcinogen (Maugh, '78). The task of this overview is to look at interactions in toxicology, excluding drug toxicology. Drug toxicology cannot be completely forgotten because many of the terms and ideas of interactions in pharmacology have entered toxicology. This presentation contains a brief outline of interactions; its definition, types and controversies. The basic intention is that of an outline. Models and approaches to assessing interactions in toxicology are also present.

Definition

The word interaction is too often used in a facile manner to confer an understanding of a sequence of biochemical events for which little or nothing is known. It is used to bridge the veiled gap between (i.e., inter-) cause and effect. An illusion is presented, analogous to the use of the word evolution, that the measured effect can be attributed to an interaction. Yet, no explanation is given to or is known of the series of biochemical events which comprise the interaction. The truth in most instances is that we do not know, as yet, the mechanisms of interactions. A discussion of interactions, more often than not, describes the measured effect with little reference to the causal mechanism.

Death is the easiest measured effect of an interaction. To gain an appreciation of the potency (i.e., toxicity) with which the interaction has ensued, toxicologists have devised the LD_{50}. The measurement of the dose-response relationship can be derived for a given toxicant by several

models, for instance, the method of Miller and Tainter ('44), Litchfield and Wilcoxon ('49), and Weil ('52). A standard protocol for deriving the LD_{50} was established as a further assurance that the estimated value of a toxicant can be obtained in all laboratories (Fed. Reg.). Changes in the LD_{50} are used as an interaction indicator (Magos, '74).

Tests in toxicology, such as acute, chronic, reproductive and teratological, provide a direct measurement of the effect of the interaction but nothing is contributed towards the mechanism of the interaction, per se.

The greatest contribution towards understanding interactions has come with the application of kinetics to a toxicant. Principally developed for use in clinical evaluation and use of drugs (Levy and Gibaldi, '75), the science of pharmacokinetics is providing a much needed stimulus in toxicology (Gehring, et al. '76). Information on the absorption, distribution, metabolism and excretion of a chemical is derived by a time plot of the data which is then applied to compartmental open models.

Results from the battery of toxicological tests and pharmacokinetics are obtained under controlled experimental conditions in which all possible parameters (i.e., temperature, humidity, stress, dose, nutrition, etc.) are regulated. The desire is understandable because without eliminating or controlling the many variables, agreement on the action of a toxicant would never be achieved. However, information derived with maximum control is not the real life situation for, in reality, the controls are reduced and the toxicants become multiples. Interactions, especially interactions of toxicants in combination, must be considered in their complexity (Magos, '76).

Finney ('52) presented mathematical models to explain the possible different effects obtained for joint interactions of biologically active chemicals. The usefulness of Finney's model was tested by Smyth, et al. ('69 and '70). Pharmacology has used the Loewe, ('53) and the approach of Chen and Ensor ('53 and '54) to analyse effects of combined drug interactions. Both of these sciences, toxicology and pharmacology, use the same terms to describe interactions and unfortunately have carried on some disagreement about the meaning of the terms " synergism", "potentiation", "sensitization" but with more agreement on the terms additive, antagonistic and independent.

Types of Interactions

The confusion surrounding synergism to describe an effect of an interaction is another example arising from a lack of understanding of the mechanics of interactions. Some authors use "the end-effect of the combination as a measure of comparison while others used the individual activities of the compounds" (Veldstra, '56). Others adhere to the epistemological meaning.

Synergism (GK. synergos) literary means "working together", "cooperation" (Rossi, '63 and Sunier, '72). Synergism in toxicology is generally accepted as being similar to that definition used in pharmacology; "the cooperative action of discrete agents, such that the total effect is greater than the sum of the two effects taken independently" (Veldstra, '56) and that adopted for epidemiology where "the risk attributable to a combined exposure exceeds the sum of the risks attributable to each exposure separately" (Rothman, '74).

Magos ('74), however, considers that when "the action can be greater than the algebraic summation" it is supplemental synergism or potentiation. He also uses the term "additive synergism" as the simple algebraic sum. Veldstra ('56) argues against the use of the term potentiation.

Interactions which produce synergistic effects are not an exception but a common occurrence. Some food additives have a synergistic toxic effect when incorporated in a purified, low fiber, diet (Ershoff, '76). Herbicides can increase the toxicity of insecticides to potencies greater than either given alone (Lichtenstein, et al. '73). Methylmercury in combination with nitrite and ethylurea reduced survival of progeny (Nixon, '77). Combinations of aflatoxin B, and Fusarium toxic, T-2, produced a synergistic lethal response (Lindenfelser, et al. '74). The herbicide silvex is degraded by the synergistic action of aquatic microorganisms (Ou and Sikka, '77). Hicks and Chowaniec ('77) studied the importance of synergy between weak carcinogens and bladder tumours.

Veldstra ('56) states that the term "potentiate" should be discontinued because it means "to endow with power" and in combination the resident "power," viz. specific activity, is not altered but "the effectiveness of the power already present is enhanced." Fingl and Woodbury ('70) agree with Veldstra that potentiation should be abandoned. Rossi ('63) notes that Webster's dictionary provides some justification for its use; potentiate - "to make potent or more effective." Scientists may be using "potentiate" in the same sense that it is employed in physics, that is, energy which is involved because of position or condition. Magos ('74) defines potentiation, also called supplemental synergism, as an action greater than the algebraic summation. The latter definition is the same as that given to synergism. Enhancement of a response by a combination of an active and an inactive compound has also been designated as sensitization (Rossi, '63). Finally, there is the often cited "synergistic" interaction of EPN and malathion although the authors referred to this interaction as a "potentiation" (Frawley, et al. '57).

Although there is some confusion about the meaning or use of potentiation, this has not impeded the publication of papers. Isopropyl alcohol and acetone potentiated the hepatotoxicity in rats of chlorinated hydrocarbons (Traiger and Plaa, '74). The chlorinated hydrocarbon, carbon tetrachloride was potentiated in rats by sodium nitrite (Suarex and Bhonsle, '74). Lead chloride and lead nitrate increased mortality in mice by enhancement of encephalitogenic potential of Langat virus (Thind & Singh, '77). Murphy reported the potentiation of toxicity of the anesthetic fluroxene by polychlorinated biphenyls.

Antagonistic interactions which eliminate an undesirable effect are the most beneficial to man. This happens when the combined effects are less than that of the active component alone. An antagonistic effect is reported for riboflavin and hepatoma induction by an azo dye (Lambooy, '76). Rats pretreated with aldrin are protected against the toxicity of parathion (Kinoshita, '74). Selenium protects against cadmium and mercury toxicity (Parizek, '76).

There is no shortage of models (i.e., procedures to be followed or emulated) to determine the effects of the various interactions, however, there

are few models that explain the interactions. The models for deriving the LD_{50} and those of pharmacokinetics have been discussed. Runner ('67) presented models to explain the various effects (e.g., synergistic, antagonistic) for concomitant teratogenic treatment. Problems of synergism and antagonism in epidemiology are discussed by Rothman ('74 and '76). Last and Cross ('78) presented a model for assessing biological effects of atmospheric pollutants on the respiratory tract, mucus-producing apparatus. A method was proposed by Carlson and Bazzaz ('77) to quantitate the concept of synergism in plants. A model to test the effect of exposure to a subtoxic challenge upon cellular integrity is described by Chin, et al. ('78). A bioassay was reported for detecting both synergistis and antagonists of paraoxon and malaoxon (Cohen and Murphy, '73).

Controversies

Undoubtedly, the most controversial subject of interactions is in chemical carcinogens. The arguments indicate how little is known about interactions at very low dosages (Maugh, '78). There presently exist two schools of thought; "one hit" hypothesis or single event and "threshold" hypothesis, or no-effect level. The former believe basically that cancer results from the interactions of one molecule of a carcinogen with a critical receptor in one cell. Models such as the probit and Mantel-Bryan extrapolations are used in this case. The other school states that there is a no-effect dose for a chemical carcinogen governed by a series of pharmacokinetic interactions before reacting with DNA. Gehring ('76) has demonstrated that the pharmacokinetics do change with different doses of a carcinogen.

Toxicological tests also deviate toward "larger than life" dosages and in so doing create a controversy over the use of super dosages. One side argues that we must obtain as much knowledge as possible about the undesirable effects of a toxicant. The other side states that these are zealous platitudes which are not the real life situations and the acquired knowledge is often misused.

Interactions in teratology and mutagenicity tests are not without their controversies. Do the same interactions which culiminate in birth defects in polytocous animals exist in man? Were not the doses given absurd? The emphasis, today, is that a chemical is, "teratogenic in the rat.....or the mouse .....or the rabbit", clearly indicating that it has not been demonstrated so in man. Similarly, the problem of extrapolating the results of mutagenicity tests to a multicellular organism.

Conclusions

It is inherent that the use of "overview" in the title of this paper will result in other aspects of interactions being overviewed. The most evident is a citation of mechanisms of interaction that are known.

Dubois, et al. ('68) provided the explanation for the synergistic effect between EPN and Malathion. This original observation had led to an understanding of the biochemical mode of action of pesticides (Corbett '74 and Wilkinson, '71 and '76). Some insight into the mechanism of carcinogenesis has been achieved. It is now thought to be a two-stage event which requires, firstly, an initiator and then a promoter (Miller, '78). Conney and Burns,

('72) reported other possible mechanisms of interaction for insecticides.

Mechanisms of interaction, briefly presented in the preceding paragraph, have not completely eluded research, however; they are complex, complicated and controversial.

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photomirex is 10-100 times more toxic than mirex and 5 times more toxic than kepone. In rat feeding studies, photomirex was observed to produce lesions in the testes, thyroid and liver of male rats. Subsequent experiments have shown that this compound causes ultrastructural alterations in the liver and testes at extremely low levels, and that the alterations persist for up to a year after photomirex exposure has ceased. Like its parent compound mirex, photomirex is also able to produce cataracts in suckling rats whose mothers are exposed to the compound. Metabolism and pharmacokinetic data have shown that photomirex is not metabolized in rats to any significant degree, and is not excreted in the bile. The main excretory route is through the feces.

Conclusions

The data presented at the meeting on photomirex indicate that this compound could have greater potential as a human health hazard than mirex. This example serves to indicate that Great Lakes Monitoring and Surveillance Programs should be designed not only to provide data on parent compounds, but also on their degradation products.

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LEAD

In its Final Report, PLUARG drew attention to its concern over the build up of lead in sediments, particularly in Lakes Erie and Ontario. Studies undertaken by PLUARG suggest that non-point sources are by far the greatest component of the load.

Concern over lead at this time arises not from any evidence that current levels of lead in drinking water or fish tissues exceed health-based regulatory standards, but because of recent evidence that inorganic lead in sediments may be transformed into more toxic organic forms by biological mechanisms in Great Lakes sediments.

The major diffuse source of lead in the Great Lakes Basin is the automobile. Alkyl lead compounds have been extensively used to improve the combustion characteristics of gasoline. When burned in the gasoline engine, most lead in gasoline is converted into inorganic form and emitted as halides which subsequently are converted during aging to oxides, sulphates and carbonates. In these compounds, lead is in particulate form and settles over the landscape as dust. Lead from automobile exhausts enters the aquatic system primarily in surface run-off although a small proportion undoubtedly

enters the lakes through atmospheric fallout and precipitation.

In 1975-76, three different groups of scientists (including one from the Canada Centre for Inland Waters, the others being in the United Kingdom and in Germany) reported that micro-organisms can methylate organic and inorganic lead compounds[1-3]. By analogy with mercury, the Committee had concern that the existence of methylated lead in the environment could lead to the recognition of hitherto unsuspected toxic effects.

The Committee reviewed the evidence relating to biomethylation of lead in the aqueous environment. It noted a recent report of the World Health Organization's Task Group on Environmental Health Criteria for Lead which concludes that:

> "Acute toxicity results in an encephalopathy that differs greatly from the effects of inorganic lead on the central nervous system. Some components of the toxic effect are probably due to the alkyl compound as a whole rather than its lead components."

The Committee concluded that the substrates, conditions and mechanisms which may lead to alkylation of lead in the environment are not known at the present time, and it recognizes the need for improvements in analytical methods and quality control procedures. Nevertheless, it considers that there is a need for exploratory measurements to be made to determine whether alkylated lead compounds are present in sediments, algae, invertebrates, fish and wildlife from the Great Lakes, and, if so, in what form and in what concentration. The Committee is willing to evaluate such data with a view to elucidating the possible health effects in order to determine whether present tolerances for lead; especially in fish, need re-evaluation. The Committee requests the Water Quality Board and the Research Advisory Board to encourage the gathering and publication of such data in conjunction with on-going monitoring efforts and to bring emerging information and analytical data to its attention.

6 RECOMMENDATIONS

During 1978, the committee proposed to both Boards, the following activities for inclusion in the IJC Regional Office program budget.

1. A Study on Intervention Guidelines for Great Lakes Environmental Contaminants in Fish

   A survey would be made of the appropriate regulatory agencies in the Great Lakes Basin to determine and document the philosophy underlying the rationale used in setting standards for individual environmental contaminants in fish.

   The assignment would be contracted to an individual familiar with the regulatory agencies concerned and with their appropriate representatives, at all levels of government affecting the Great Lakes. Hence, a period of extensive travelling would be anticipated by the consultant.

   The study would aid in clarifying cases of disparity among different agencies by delineating and comparing the criteria used in deriving their standards.

   Estimated cost of this study - $10,000 (FY 79/80).

2. A Workshop on the Interaction of Toxic Chemicals of Concern in the Great Lakes Ecosystem - $15,000 (FY 80/81)

   Models are currently under development to evaluate the toxicity of exposure to mixtures and verification of the models is necessary for predicting the combined effects of the compounds present. Based on acute toxicity data for the individual chemicals, prediction of their joint action has been possible but is presently limited to handling two or three interacting compounds at one time.

   The workshop is intended to review the current state of knowledge concerning these predictive models, the nature of their data requirements, and the limitations of their application. In addition, the results of this activity will complement the Water Quality Board's list of chemicals found in the Great Lake ecosystem and will aid in the process of identifying and quantifying potential toxicological effects of interactions.

MEMBERSHIP LIST

JOINT SCIENCE ADVISORY BOARD/WATER QUALITY BOARD COMMITTEE
ON THE
ASSESSMENT OF HUMAN HEALTH EFFECTS OF GREAT LAKES WATER QUALITY

Mr. J. R. Hickman (Chairman)
Director, Bureau of Chemical Hazards
Health and Welfare Canada
Environmental Health Centre
Ottawa, Ontario

Dr. J. H. Aitken *(Until March 1979)*
Ontario Ministry of Labour
Toronto, Ontario

Dr. G. C. Becking *(Effective March 1979)*
Chief, Environmental Toxicology Div.
Dept. National Health and Welfare
Environmental Health Centre, Room 118
Ottawa, Ontario

Dr. G. Berg
Chief of Virology
Advanced Wastewater Treatment Res. Lab.
U.S. Environmental Protection Agency
National Environmental Research Center
Cincinnati, Ohio

Dr. Rita Bogoroch, Director
Health Effects Program
National Council of the Paper Industry for
Air & Stream Improvement (NCASI)
New York, New York

Dr. N. Chernoff
Health Effects Research Lab., MD-74
U.S. Environmental Protection Agency
Research Triangle Park, N.C.

Dr. James H. Day
Department of Medicine
Queen's University
Kingston, Ontario

Dr. R. W. Durham
Applied Research Division
Canada Centre for Inland Waters
Dept. of Fisheries and Environment
Burlington, Ontario

Dr. H. L. Falk
Associate Director for Health
Hazard Assessment,
N.I.E.H.S.
Research Triangle Park, N.C.

Dr. G. Wolfgang Fuhs, Director
Division of Laboratories and
Research
N.Y. State Dept. of Health
Environmental Health Center
Tower Building, Empire State Plaza
Albany, New York

Dr. Rolf Hartung
School of Public Health 1
University of Michigan
Ann Arbor, Michigan

Dr. Harold E. B. Humphrey
Environmental Epidemiologist
State of Michigan
Department of Public Health
Lansing, Michigan

Dr. G. J. Stopps
(Until March 1979)
Department of Preventive Medicine
University of Toronto
Toronto, Ontario

ASSESSMENT OF HUMAN HEALTH EFFECTS OF GREAT LAKES WATER QUALITY

(Continued)

Mrs. Ann H. Vajdic *(Effective March 1979)*
Microbiologist
Water Technology Section
Pollution Control Planning Branch
Ontario Ministry of the Environment
Toronto, Ontario

SAB Liaison Member
Dr. Mitchell R. Zavon
Medical Director
Hooker Chemicals
Niagara Falls, New York

Observers
Mr. Joseph Prince
Technical Support Section
U.S. Environmental Protection Agency
Region V, Water Division
Chicago, Illinois

Dr. Lyman Condie
Toxic Substances Coordinator
U.S. Environmental Protection Agency
Region V
Chicago, Illinois

Secretariat Repsonsibilities
Dr. A. E. P. Watson
Research Scientist
International Joint Commission
Great Lakes Regional Office
100 Ouellette Avenue, 8th Floor
Windsor, Ontario